Penile lesion in end-stage renal failure — cancer or otherwise?: Calcific uremic arteriolopathy presenting with a penile lesion

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Abstract

Calcific uremic arteriolopathy or calciphylaxis is a rare condition that can present with clinical features similar to penile cancer. It is a diagnosis to consider in patients with end-stage renal failure (ESRF) presenting with a penile lesion. We describe one such case, where a patient with ESRF presented with a solid, tender penile mass and underwent surgery for presumed penile cancer. Histopathological analysis however confirmed a diagnosis of calcific uremic arteriolopathy, without evidence of malignancy. The clinical diagnosis of calcific uremic arteriolopathy relies on a high index of suspicion, and lesion biopsy is controversial due to a high risk of poor wound healing and sepsis. New treatment options are encouraging, and have been reported, albeit in small numbers. Delayed diagnosis can adversely affect both quality of life and prognosis in a condition with an extremely high mortality rate.

Introduction

Calcific uremic arteriolopathy is a condition characterized by obstructive vasculopathy, with calcification of small arteries and arterioles resulting in luminal occlusion and subsequent cutaneous necrosis. Found typically in patients with end-stage renal failure (ESRF), it has an incidence in those on hemodialysis of 1% to 4%.[1] Diagnosis carries an appalling prognosis with a mean time to death of 2.5 months,[2] and management is often suboptimal due to inadequate awareness of the disease. With a growing number of patients with ESRF and an increasing awareness of the condition, it is to be expected that there will be a proportionate increase in the number of patients who develop calcific uremic arteriolopathy. We describe one such patient who was referred to urology with a penile lesion.

Case report

A 61-year-old Caucasian man was admitted to hospital with a blocked long-term urethral catheter, required to manage his benign prostatic enlargement. His comorbidities included ESRF (secondary to diabetic nephropathy) requiring hemodialysis, ascites, and peripheral vascular disease with multiple previous toe amputations. On examination, he had a tight phimosis, slough on the tip of the glans, and an extremely tender hard glanular mass. Examination of his lower limbs revealed an ulcerated head of the first metatarsal of his right foot. His medications included calcium containing vitamin D analogues, calcium supplements, and erythropoietin.

Laboratory results revealed mildly elevated inflammatory markers and ESRF. Serum calcium was normal at 2.27 mmol/L, and serum phosphate was raised at 2.7 mmol/L giving a calcium phosphate product of 75.9 mg/dL (normal range: 20.6–52.5 mg/dL). The patient's parathyroid hormone level was persistently elevated at 16.2 nmol/L, and 1 month previously this level had been 72 nmol/L (normal range: 1.3–6.8 nmol/L), showing secondary hyperparathyroidism.

Due to progression of peripheral vascular disease, an ultrasound scan of vasculature in the lower legs was undertaken, demonstrating extensive calcification in the arteries of both calves. Suspected fluid overload led to an echocardiogram, which showed heavy mitral annular calcification.

Penile malignancy was suspected, and so he was referred to the supra-regional penile cancer centre, where it was determined that malignancy with corpora cavernosa invasion was the most likely diagnosis. He subsequently underwent dorsal slit under local anesthetic to visualize and determine the extent of disease. He was found to have a completely destroyed glans, replaced with necrotic sloughy tissue. This was debrided and a biopsy of the corpora cavernosa was taken for diagnosis. The corporal biopsy did not bleed and clinically was consistent with ischemic fibrosis rather than cancer.

Microscopically, histopathology did not reveal malignancy, but tissue necrosis, widespread luminal compression secondary to vascular calcification, hyperplasia of the tunica intima, and inflammatory cell infiltration – consistent with a diagnosis of calcific uremic arteriolopathy. Immediate postoperative recovery was uneventful, and the patient was discharged to the referral centre for ongoing management of his renal disease. Soon afterwards, poor wound healing was noted, and the patient passed away with overwhelming sepsis about 1 month postoperatively.

Discussion

Calcific uremic arteriolopathy is not completely understood, with a multifactorial pathogenesis. It occurs almost exclusively in patients with ESRF, where there is an imbalance between inducers and inhibitors of calcification in the vascular wall. High serum phosphate facilitates transformation of vascular smooth muscle into osteoblast-like-cells – encouraging calcification. Uremia creates an inflammatory reaction that further suppresses calcification inhibitors. In previously reported cases, 76% of patients with penile necrosis secondary to calcific uremic arteriolopathy have concurrent diabetes, compared to 39% of ESRF patients, which could suggest that diabetes is a predisposing factor.[2] Two-thirds of patients with penile calcific uremic arteriolopathy have extra-genital gangrenous lesions,[2] showing that calcification is often extensive and present throughout the body. Other risk factors that have been linked with calcific uremic arteriolopathy include female gender, mineral and bone disorders, obesity, warfarin anticoagulation, and Caucasian ethnicity.[3]

The presentation of calcific uremic arteriolopathy in the early stages is typically with dysesthesia, progressing to an erythematous, violaceous rash similar to livedo reticularis. This then evolves to exquisitely painful eschars, most commonly on the lower limbs.

Diagnosis should ideally be made from clinical presentation, metabolic parameters, and imaging. A potential diagnostic indicator is a calcium phosphate product over 70 mg/dL,[2] as it has been demonstrated that those with penile calcific uremic arteriolopathy had a significantly higher calcium phosphate product than a control group of patients with ESRF ($p < 0.05$).[2] Biopsy has been used in the past for diagnosis, however more recently this has been discouraged. Biopsy carries a high risk of poor healing, sepsis, and necrotic spread. Surgical stress is thought to lead to increased activation of the sympathetic nervous system, resulting in circulatory disturbance and necrotic progression.[4] This is why surgery is generally only reserved for those with intractable pain, after the failure of conservative management. First-line conservative measures include aggressive wound care, systemic antibiotics, non-calcium containing phosphate binders, cinacalcet (a calcium-receptor stimulating agent), bisphosphonates and, the most promising of all, sodium thiosulfate. Sodium thiosulfate has been shown to successfully treat calcific uremic arteriolopathy with clinical improvement within 2 weeks, and complete resolution of pain after 8 months of treatment.[5] It is thought to work by dissolving previously insoluble calcium in tissues as calcium thiosulfate,[6] while inducing endothelial nitric oxide synthesis promoting circulatory normality.[7]

Conclusion

Calcific uremic arteriolopathy is a rare diagnosis, but one that is being increasingly reported with growing numbers of patients with ESRF. It is a diagnosis that relies on a high degree of clinical suspicion, and this case raises awareness of the condition for urologists who may be asked to review penile lesions in patients with positive risk factors. This case report offers a reminder to consider this diagnosis even when there is strong clinical suspicion for penile malignancy. The diagnosis of calcific uremic arteriolopathy is especially important on account of the potentially adverse consequences of suboptimal management for these patients. If the condition is detected early, there is a far greater chance of clinical improvement, improved quality of life, and disease resolution.

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